REMARKS

Claims 1-9 and 11-22 are pending. Claims 23-30 have been withdrawn as being directed to a non-elected invention. Claims 1-9 and 11-22 are currently under examination in the present application. All of the claims under examination stand rejected. Claims 1, 2, and 11-22 are amended herewith. Support for these amendments can be found throughout the specification. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

The Office Action

Claims 1-9 and 11-21 were rejected under 35 U.S.C. § 102(b) as being completely anticipated by the British Patent Application (GB 1570597) (hereinafter "GB '587"). Claims 1-9 and 11-22 were also rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over GB '587. Applicants respectfully traverse the foregoing rejections.

Comments on the Prior Response

The rejection acknowledges applicants response filed in paper No. 18. The rejection states that the case law cited by the applicants is not related to the current issues. The rejection states that *In re Henze* is not applicable because a methyl group and a phenyl group are structurally different. The rejection concludes that the present case is different because the difference between the present claims and the prior art is only one carbon atom. Applicants respectfully disagree.

Applicants submit that its discussion of the case law in its prior response was indeed related to the issues in the present case and incorporates that discussion herein by reference. Applicants have distinguished on the facts those cases relied upon by the examiner as support for a finding of *prima facie* obviousness in the present case. And, contrary to the examiner's statement, applicants submit that *In re Henze* supports allowance of the present

claims. Furthermore, applicants submit that the present claims do not differ from the prior art by only one carbon atom. Applicant's discussion of that issue in their prior response is also incorporated herein by reference. Discussion of that issue with respect to the present rejection will be discussed below.

The Rejection Under 35 U.S.C. §102(a)

Claims 1-9 and 11-21 were rejected under 35 U.S.C. §102(b) as being completely anticipated by GB '587. The rejection states that the GB '587 discloses 16 alkyl and alkenyl estradiols and further states that those compounds are presently claimed. The rejection references portions of GB '587 and the compounds drawn on pages 2 to 4 of the Office Action, and contends that those compounds are presently claimed. Applicants respectfully disagree.

The compounds drawn on pages 2-4 of the Office Action are 16-methyl estradiol, 16-ethyl estradiol, 16-butyl estradiol, 16-propyl estradiol and 16-allyl estradiol. GB '587 discloses 16-alkyl and alkenyl estradiols. Applicants submit that none of these compounds is covered by the present claims.

The present claims require the compound to be substituted at both the 2-position and the 16-position. Neither the compounds drawn on pages 2-4 of the Office Action nor the compounds disclosed in GB '587 disclose substitution at both the 2-position and the 16-position. The compounds drawn on pages 2-4 of the Office Action and disclosed in GB '587 are unsubstituted at the 2-position. By contrast, the present claims require substitution at the 2-position with "$-N_3$, $-C\equiv N$, $-C\equiv C-R$, $-CH=CH-R$, $-R-CH=CH_2$, $-C\equiv CH$, $-O-R$, $-R-R_1$, $-OC(O)CH_3$, $-C(O)H$, $-NH_2$, $-NMe_2$, $-NHMe$, or $-O-R-R_1$ where R is a straight or branched alkyl with up to 10 carbons or aralkyl, and R_1 is $-OH$, $-NH_2$, $-Cl$, $-Br$, $-I$, $-F$ or CF_3." None of these substituents are disclosed in the compounds drawn on pages 2-4 of the Office Action or in GB '587.

In order for a reference to anticipate a claim, the reference must disclose every element of the claim. Since GB '587 does not disclose substitution at both the 2- and the 16-position, GB '587 cannot anticipate the present claims. Therefore, applicants submit that it is improper to reject the present claims under 35 U.S.C. §102(b) in view of GB '587. Accordingly, applicants request withdrawal of the present rejection under 35 U.S.C. §102(b).

The Rejection Under 35 U.S.C. §103(a)

Claims 1-9 and 11-22 were also rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over GB '587. The rejection states that the references teach 16-estradiol derivatives, which embrace the presently claimed invention. The rejection also states that the instant claims differ from the reference in claiming a broader scope than the prior art. The rejection further states that the instant claims are considered obvious when in the prior art R_1 represents alkyl or alkenyl group and R_2 is H. The rejection concludes that it would have been obvious to one skilled in the art to prepare additional beneficial compounds useful as anti-estrogen drugs having an alkyl or alkenyl group at 16-position of estradiol because the prior art teaches the same groups and specific compounds at the 16-position. The rejection further states that motivation to prepare alkyl or alkenyl derivatives is taught.

What the present rejection ignores is that GB '587 provides no motivation for substitution at both the 2-position and the 16-position. The compounds drawn on pages 2-4 of the Office Action are 16-methyl estradiol, 16-ethyl estradiol, 16-butyl estradiol, 16-propyl estradiol and 16-allyl estradiol. GB '587 discloses 16-alkyl and alkenyl estradiols. The present claims, however, require the compound to be substituted at both the 2-position and the 16-position. Neither the compounds drawn on pages 2-4 of the Office Action nor the compounds disclosed in GB '587 disclose substitution at both the 2-position and the 16-position. The compounds drawn on pages 2-4 of the Office Action and disclosed in GB '587 are unsubstituted

at the 2-position. By contrast, the present claims require substitution at the 2-position with "-N_3, -C≡N, -C≡C-R, -CH=CH-R, -R-CH=CH_2, -C≡CH, -O-R, -R-R_1, -OC(O)CH_3, -C(O)H, -NH_2, -NMe_2, -NHMe, or -O-R-R_1 where R is a straight or branched alkyl with up to 10 carbons or aralkyl, and R_1 is -OH, -NH_2, -Cl, -Br, -I, -F or CF_3." None of these substituents are disclosed or suggested in the compounds drawn on pages 2-4 of the Office Action or in GB '587. Furthermore, none of the substituents presently claimed for the 2-position differ from GB '587 by only "one carbon atom," as the present rejection suggests. Thus, none of the compounds presently claimed are homologues of the compounds disclosed in GB '587.

Respectfully, Applicants submit that a showing of *prima facie* obviousness has not been established by the Examiner because, among other reasons, the cited art does not teach or suggest the problem nor the source of the problem which Applicants have identified. *See In re Peehs*, 612 F.2d 1287, 204 USPQ 835 (CCPA 1980); *In re Zurcko* 111 F.3d 887, 42 USPQ2d 1476 (Fed. Cir. 1997).

Applicants recognized and identified the problems of 2-methoxyestradiol being metabolized to the much less active metabolite 2-methoxyestrone, *and* being deactivated by an additional metabolic deactivation pathway that results in the glucuronidation of 2-methoxyestradiol. *See* specification page 10, line 34-page 11, line 27. To solve this problem, Applicants' invention *adds steric bulk and/or modification of electrostatic characteristics at the 16-carbon* of 2-methoxyestradiol, to retard or prevent interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate. See Specification at page 11, lines 16-27. Further, the addition of steric bulk and/or electrostatic modification at the 16-carbon may retard or prevent glucuronidation. *Id.* It is believed that retardation or prevention of these two metabolic deactivation pathways prolongs the serum lifetime of 2-methoxyestradiol and other estrogenic compounds while retaining the desired anti-angiogenic and anti-tumor activity. *See*

specification, page 11, lines 16-27. Indeed, initial screening of epimeric 16-ethyl-2-methoxyestradiol and related analogues showed that it is about equipotent to 2-methoxyestradiol in inhibition of HUVEC cell proliferation *in vitro*. *See* specification, page 17, lines 2-6.

None of the prior art of record discloses, and specifically GB '587 does not disclose the problem discovered by applicants; *i.e.*, deactivation of the anti-angiogenic effects of estradiol derivatives by metabolic processes. In the absence of an appreciation of the problem, the solution of the problem is clearly nonobvious.

Furthermore, Section 2144.09 of the MPEP discusses the subject of close structural similarity between chemicals. Although the present claims do not involve homologues, the MPEP makes it clear that even if compounds are homologous, homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed "as a whole." MPEP §2144.09. Thus, it would be erroneous for the examiner to contend that the present claims are *prima facie* obvious merely because of alleged homology or structural similarity. The examiner must consider the claimed invention and the prior art as a whole in making a determination of alleged obviousness. Thus, the problem of deactivation discovered by applicants and the solution of that problem by substituting estradiols at both the 2- and the 16-position to provide bulk hindrance to deactivation mechanisms must also be considered.

To illustrate how the claimed invention and the prior art must be considered as a whole, the MPEP discusses the case of *In re Langer*, 465 F.2d 896 (CCPA 1972). The MPEP states, "Claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from the claimed

amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class.)." MPEP §2144.09.

The same principal of law is applicable in the present case. In the present case the prior art does not disclose sterically hindering degradation of the hydroxyl group substituted at the 17-position by using bulk-hindering substituents substituted at the 16-position. Although GB '587 discloses substitution at the 16-position, there is no disclosure that it is to preserve anti-angiogenic activity. In fact, GB '587 does not disclose that its compounds have any anti-angiogenic activity. Rather, GB '587 discloses that its compounds have anti-estrogen activity (it should also be noted that the compounds disclosed in GB '587 are not substituted at the 2-position). Therefore, the prior art fails to teach the concept of using bulk hindrance at the 16-position to protect against anti-angiogenic deactivation of the claimed estradiol derivatives.

Furthermore, the properties of the steroidal molecules at issue here are unpredictable based upon structural similarity. For example, 2-methoxy estradiol is anti-angiogenic and is useful for treating diseases such as cancer; whereas, 4-methoxy estradiol is a known carcinogen and would not be useful for treating cancer or any other disease in a human. Thus, the mere shift of the methoxy group from the 2-position to the 4-position significantly changes the properties of the estradiol derivative, and, therefore, illustrates the unpredictability of the properties of this molecule based upon structural similarity.

The MPEP states that, "The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (appellant produced sufficient evidence to establish a substantial degree of unpredictability in the pertinent art area, and thereby rebutted the presumption that structurally similar compounds have similar properties)." MPEP §2144.09.

Applicants submit that the foregoing showing of unpredictability overcomes any alleged *prima facie* obviousness of the presently claimed compounds.

Applying the rulings of the CCPA (the predecessor court of the Federal Circuit) in *In re Langer* and *In re May* to the facts of the present case and considering the prior art and the claimed invention as a whole dictates a finding of nonobviousness of the presently claimed invention. Therefore, the rejection of the present claims under 35 U.S.C. § 103 as being obvious in view of GB '587 is improper and should be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully maintain that Claims 1-9 and 11-22 are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404-745-2408 is respectfully solicited.

Respectfully submitted,

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